REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims presented herein.

I. Status of the Claims

In this Amendment B, claims 1 and 4 have been amended in order to more particularly claim certain embodiments of the present application. Additionally, claims 27-35 have been added.

Accordingly, upon entry of this Amendment B, claims 1-4, 6, 8 and 10-35 will be pending. Claims 8, 12 and 21-26 remain withdrawn from consideration at this time, for being directed to non-elected subject matter. As such, claims 1-4, 6, 10, 11, 13-20 and 27-35 are currently under examination.

Claim 1 has been amended to more particularly define the R_4 substituent of Formula II, so that R_4 is independently hydrogen or a linear or branched (C_1-C_8) alkyl residue. Support for this amendment may be found, for example, in paragraph [0020] of the published application (U.S. 2008/0317675 A1).

Claim 4 has been amended to more particularly define the R_4 substituent of Formula II, so that R_4 is independently hydrogen or a linear or branched (C_1-C_8) alkyl residue. Support for this amendment may be found, for example, in paragraph [0020] of the published application. Further, claim 4 has been amended to more particularly define the substituents of Formula II, so that each R_1 is independently (i) hydrogen, (ii) a linear or branched (C_1 – C_8) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroalkoxy groups or combinations thereof, or (iii) the residue of a carbohydrate.

Independent claim 27 has been added and requires a composition for use in a diagnostic imaging procedure. The composition comprises iosimenol and at least one monomer selected from the group consisting of ioversol, iohexol, and iopamidol. Support for this amendment may be found, for example, in paragraphs [0032], [0039],[0040], [0048] and [0053] of the published application.

Claim 28 has been added and requires the at least one monomer of claim 27 to comprise ioversol. Support for this amendment may be found, for example, in paragraph [0040] of the published application.

Claim 29 has been added and requires the at least one monomer of claim 27 to comprise iohexol. Support for this amendment may be found, for example, in paragraphs [0040] and [0053] of the published application.

Claim 30 has been added and requires the at least one monomer of claim 27 to comprise iopamidol. Support for this amendment may be found, for example, in paragraph [0040] of the published application.

Claim 31 has been added and requires the composition of claim 27 to further comprise a pharmaceutically acceptable vehicle. Support for this amendment may be found, for example, in paragraphs [0042] and [0043] of the published application.

Claim 32 has been added and requires the pharmaceutically acceptable vehicle of claim 31 to be selected from the group consisting of aqueous buffer solutions, sterile water for injection, physiologic saline, balanced ionic solutions, a chelating agent, and other non-radioactive additives comprising excipients and anticlotting agents. Support for this amendment may be found, for example, in paragraph [0042] of the published application.

Claim 33 has been added and requires the aqueous buffer solutions of claim 32 to be selected from the group consisting of tris(hydroxyethyl)amino methane and salts thereof, phosphate, citrate and bicarbonates; the balanced ionic solutions to be selected from the group consisting of chlorides and bicarbonates of cations selected from the group consisting of Ca, Na, K, and Mg, and other halides, carbonates, sulphates, phosphates of Na, K, Mg and Ca; the chelating agents to be selected from the group consisting of H_4EDTA, $EDTACaNa_2$ and calcium monosodium DTPA-BMEA; the excipients to be selected from the group consisting of glycerol, polyethylene glycol and dextran; and, the anticlotting agent to be selected from the group consisting of heparin and hirudin. Support for this amendment may be found, for example, in paragraph [0042] of the published application.

Claim 34 has been added and requires the composition of claim 27 to comprise an additional contrast agent different than the at least one monomer and the iosimenol as required in claim 27. Support for this amendment may be found, for example, in paragraph [0041] of the published application.

Claim 35 has been added and requires the additional contrast agent of claim 34 to be selected from the group consisting of X-ray contrast agents, magnetic resonance imaging agents, radionuclide imaging agents, ultrasound imaging agents, and optical imaging agents. Support for this amendment may be found, for example, in paragraph [0041] of the published application.

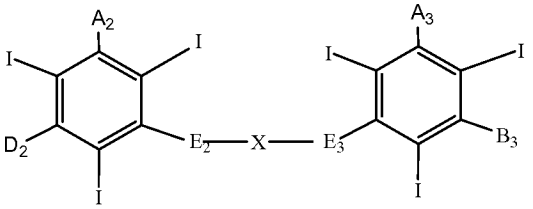
II. The Pending Claims Are Not Obvious

Applicant requests reconsideration of the rejection of claims 1-4, 6, 8, 10, 11 and 13-20 as unpatentable under 35 U.S.C. § 103(a) over Felder (US 5,695,742) in view of Sovak (US 5,698,739).

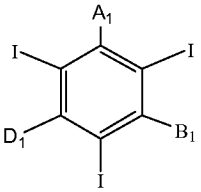
A. The Claimed Subject Matter and Felder and Sovak

(i) The Claimed Subject Matter

Claim 1, from which all other rejected claims depend, is directed to an injectable radiological composition for x-ray visualization during radiological examinations. The composition comprises a pharmaceutically acceptable vehicle and a mixture of at least one monomer (corresponding to Formula I) and at least one dimer (corresponding to Formula II):



Formula (II)



Formula (I)

wherein, with regard to Formula I:

A_1 and B_1 are $-CON(R_3)R_1$;

D_1 is $-N(R)C(O)R_2$;

each R and R_2 is independently H, or a linear or branched (C_1-C_8) alkyl residue, optionally substituted by one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_1 is independently (i) hydrogen, or (ii) a linear or branched (C_1-C_8) alkyl residue, optionally substituted with one or more hydroxy, alkoxy, hydroxyalkoxy groups or combinations thereof;

each R_3 is independently linear or branched (C_1-C_8) alkyl residue, optionally substituted with one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

and wherein with regard to Formula II:

A_2 and A_3 are $-CONH_2$;

B_3 and D_2 are $-CON(R)R_1$;

E_2 and E_3 are independently selected from the group consisting of $-CON(R)-$, $-N(R)C(O)-$ and $-N(COR_2)-$;

each R is independently H, or a linear or branched (C_1-C_8) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_1 is independently (i) hydrogen, (ii) a linear or branched (C_1-C_8) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof, or (iii) the residue of a carbohydrate;

or R and R_1 are each members of a (C_3-C_7) cyclic residue further comprising the nitrogen atom to which each of R and R_1 is bonded, said cyclic residue being optionally interrupted by -O-, -S- or $-NR_4-$, and/or optionally substituted by one or more hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_2 is independently a linear or branched (C_1-C_8) alkyl residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_4 is independently hydrogen or a linear or branched (C_1-C_8) alkyl

residue, optionally substituted by one or more hydroxyl, alkoxy or hydroxyalkoxy groups or combinations thereof; and

X is a bond or a linear or branched (C_1-C_8) alkylene chain which is optionally substituted by up to six hydroxyl groups, said alkylene chain being optionally interrupted by -O-, -S-, -NR_4- or -N(R)C(O)- groups.

As noted in the present application, Applicant has discovered that novel monomer-dimer mixtures, wherein the dimer (of Formula II) has at least one primary carboxamide substituent (and in various embodiments may have two primary carboxamide substituents, as currently recited in claim 1) and the monomer (of Formula I) does not contain any primary carboxamide substituents, have unexpectedly and favorably lower osmolality and viscosity values than would be predicted based solely upon the contribution of the monomer and dimer in the mixture. More notably, Applicant has surprisingly found that compositions arising from such monomer-dimer mixtures have favorable intermolecular attractions (between the dimers of Formula II and the monomers of Formula I). This appears to result in intermolecular aggregation, thereby reducing the effective number of particles present in the solution and hence the osmolality of the mixture, as well. (See, e.g., para. [0025].)

(ii) Felder

Felder generally discloses an injectable aqueous formulation containing radiopaque contrast agents useful for X-ray imaging of a human or animal body. (See, e.g., the Abstract.) More particularly, Felder discloses injectable aqueous solutions that comprise mixtures of non-ionic and water-soluble iodinated aromatic compounds, preferably constituted by: (a) compounds comprising an aromatic nucleus which is at least triiodo-substituted; and, (b) compounds comprising at least two aromatic nuclei variably bound together, each one at least triiodo-substituted. (See, e.g., col. 1, lns. 15-22.) Felder further discloses two alternative or different ways to decrease osmolality. The first is by keeping the total iodine content of aqueous solutions between a desired range, which favors molecular aggregation.[1] The second is to increase the number of atoms of iodine per molecule by covalently binding together two or more triiodonated aromatic nuclei through suitable alkylenic bridges, functionally substituted or not, to obtain the oligomeric structures, thus reducing the number of particles in solution. (See, e.g.,

[1] Aggregation is known in the art and generally refers to the tendency of large molecules to combine in clusters or clumps. (See, e.g., Hawley's Condensed Chemical Dictionary, 13th Edition, page 26.)

col. 2, lns. 30-37.) It is through the second approach (i.e., reducing the number of particles in the solution) that Felder attempts to lower osmolality. Finally, Felder discloses that ioversol can be used as the monomer in the oligomeric mixture.

As recognized by the Office, Felder fails to disclose or suggest combining ioversol with a dimer that falls within Formula II of pending claim 1 (e.g., such as iosmin). Recognizing this deficiency, the Office combines Felder with Sovak in an attempt to render the subject matter of Applicant's claim 1 obvious.

(iii) Sovak

Sovak discloses triiodo-5-aminoisophthaldiamides that provide low viscosity and low osmolality. (See, e.g., the Abstract.) The compositions can be used as non-ionic radiographic contrast media. Sovak discloses that iosmin (or iosimenol) can be used as a dimeric compound in the compositions.

B. The Claimed Subject Matter is not Obvious

The Office has maintained the rejection of the pending claims over Felder in view of Sovak for the reasons of record in the Office action mailed on July 7, 2010. Specifically, the Office maintains that it would have been obvious to one of ordinary skill in the art to incorporate the dimers (e.g., iosmin) as disclosed by Sovak into the composition disclosed by Felder because Sovak teaches that the dimers of Applicant's Formula II are stable in aqueous solutions, readily form supersaturated solutions which remain stable, have good biological tolerance and have a high iodine content. (See, e.g., pages 5-6 of the July 7, 2010 Office action.) For the reasons set forth below, Applicant respectfully disagrees.

Specifically, Applicant submits that one of ordinary skill in the art would lack motivation to combine the monomers of Felder with the dimers of Sovak in order to arrive at the composition required in Applicant's claim 1. In particular, Applicant notes that one of ordinary skill in the art would readily ascertain that Felder and Sovak utilize distinctly different mechanisms to affect osmolality and would therefore clearly lack any reason or motivation to combine the teachings of these references.

Felder, for instance, uses a mixture comprising a monomer and dimer to decrease the osmolality of the compositions disclosed therein. Felder attempts to achieve this goal by reducing the number of particles in solution (i.e., solvated particles). Applicant maintains that a person of ordinary skill in the art would understand this to be the case based upon the dimers disclosed by Felder in Table 3. Specifically, it is to be noted that Table 3 (along with the Working Examples) provides the only list of specific compounds (rather than the general disclosure of numerous combinations provides in the claims and the Summary of the Invention). In each of these specifically disclosed compounds, the "A" groups of the dimers are large (i.e., secondary or tertiary, rather than primary, nitrogen atoms), and thus sterically shield the adjacent iodine moieties (at least more so than a primary nitrogen atom). Furthermore, these large "A" groups contain at least 2 hydroxyl (OH) groups, which increase hydrophilicity and thereby aid with water solubility. It is clear, then, that the dimers of Felder seek to affect osmolality by reducing the number of particles in solution.

Sovak, conversely, attempts to reduce the osmolality of the compositions disclosed therein by aggregation. Specifically, Applicant notes that one of ordinary skill in the art would readily understand that the dimers disclosed in Sovak use primary carboxamide groups, which are small and which do not sterically shield the adjacent iodine moieties, thus producing hydrophobic regions in the contrast media molecules. As such, one of ordinary skill in the art would further understand that the dimers in Sovak (as well as those recited in Applicant's claim 1) affect osmolality by means of aggregation, rather than by means of a reduction in the number of solvated particles (as in Felder).

As Felder and Sovak teach distinctly different mechanisms to affect osmolality, Applicant maintains that one having ordinary skill in the art would clearly lack a reason/motivation to combine the teachings of these references. That is, one of ordinary skill in the art would expect that a combination of the monomers disclosed by Felder with the dimers disclosed by Sovak in a solution in which the dimers affect osmolality through the mechanism of aggregation would actually disrupt the aggregation and lead to an increase in osmolality. In particular, it is to be noted that the monomers of Formula I in Applicant's claim 1 do not include primary carboxamide moieties (i.e., $-CONH_2$ moieties), and thus do not contain exposed iodine moieties or the hydrophobic regions related thereto. As a result, one having ordinary skill in the art would have thought that the monomers detailed in claim 1 would actually disrupt aggregation of the dimers, thus having a detrimental effect on osmolality (i.e., increasing osmolality). As such, there is no

reason or motivation for one having ordinary skill in the art to combine the monomers of Felder with the dimers of Sovak in an attempt to arrive at each and every element of Applicant's claim 1.

Moreover, Applicant submits that, because it would not have been obvious to use the dimers of Sovak in the composition of Felder due to the individual teachings of these references, one of ordinary skill in the art would have expected the osmolality of the composition to actually be higher than the theoretical value, as a result of disruption to dimer aggregation. As a result, Applicant has identified a surprising result with the combination of the formulas in claim 1. Stated another way, in contrast to what one of ordinary skill in the art would have expected when the monomer and dimer of claim 1 are combined, Applicant has surprisingly found that the composition of claim 1 actually shows an osmolality similar to Applicant's theoretically determined osmolality.

Notably, the theoretical values of exemplary monomers and dimers are presented in Table 2 of the published application. These values were calculated based on the percentage contributions from the pure samples of the dimer alone and the monomer alone and therefore assume no disruption of the aggregation. The results of the comparison of osmolality vs. theoretical osmolality are illustrated graphically in the attached Exhibit A (submitted with this Amendment B). As noted above, one having ordinary skill in the art would have expected that using dimers of Applicant's Formula (II) in combination with monomers of Applicant's Formula (I) would adversely affect aggregation and therefore increase the osmolality compared to the use of the dimers alone. As such, one having ordinary skill in the art would further expect the measured osmolality for each dimer concentration of Table 2 to be higher than the theoretical value. However, as shown in Exhibit A (and as disclosed in Table 2), the osmolality is not increased above the theoretical value. As noted in the published application (see, e.g., paragraph [0025] therein), this is a surprising result and contrary to what one having ordinary skill in the art would have expected.

Accordingly, for the reasons stated above, Applicant respectfully submits that one having ordinary skill in the art would not have a reason or motivation to substitute the dimers of Felder with the dimers of Sovak with an expectation of providing an alternative composition having an osmolality similar to the theoretical osmolality for the composition. Instead, one having ordinary skill in the art would have expected such a combination to have a significantly higher osmolality

than the theoretical value as a result of disruption of the dimer aggregation. Applicant has surprisingly found, however, that a composition comprising a monomer of Formula (I) and a dimer of Formula (II) yields an osmolality below the theoretical value.

In view of the foregoing, Applicant respectfully submits that the subject matter of claim 1, as well as all claims depending therefrom, is patentable over the combination of Felder and Sovak. Reconsideration of these rejections is therefore requested.

CONCLUSION

In view of the foregoing, Applicant respectfully requests reconsideration and allowance of all pending claims.

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 01-2384 for any fees due in connection with the submission of this Amendment B, including a one (1) month extension of time, as well as (i) any excess claims fees and (ii) the fee for Applicant's Request for Continued Examination being filed simultaneously herewith.

Respectfully submitted,

/ Derick E. Allen /

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